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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,205	11/14/2006	Nicholas S. Bodor	005192-000024	4092

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EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
04/04/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/551,205	BODOR ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35 and 56-98* is/are pending in the application.

4a) Of the above claim(s) *13-35 and 67-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,56-66 and 82-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :11 pgs / 14Nov2006, 10Aug2007, 8Nov2007, 4Jan2008.

DETAILED ACTION

This application is the national stage entry of PCT/US04/09387, filed 26 Mar 2004; and claims benefit of provisional application 60/458,922, filed 28 Mar 2003; and claims benefit of provisional application 60/484,756, filed 02 July 2003; and claims benefit of provisional application 60/541,247, filed 04 Feb 2004.

Claims 1-35 and 56-98 are pending in the current application. Claims 13-35 and 67-81, drawn to non-elected inventions, are withdrawn. Claims 1-12, 56-66, and 82-98 are examined on the merits herein.

However, the parent applications provisional application 60/458,922, filed 28 Mar 2003; provisional application 60/484,756, filed 02 July 2003; and provisional application 60/541,247, filed 04 Feb 2004; upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for the instant claims 1-12, 56-66, and 82-98 of this application since parent applications 60/458,922, filed 28 Mar 2003; and 60/484,756, filed 02 July 2003 are not seen to disclose the amorphous cladribine-cyclodextrin complex of in the independent claims 1, 56 and 82. Written description for claims 1-11 and 56-65 may be found in provisional application 60/541,247, filed 04 Feb 2004, however no support is found for the percent by weight present in the inclusion complex and the non-inclusion complex of instant claims 12 and 66, the temperature range of about 40 to about 80 °C of claims 82 and 83, the temperature range of about 45 to about 50 °C of claim 85, or the temperature range of about -40 to about -80 °C of claim 89. Thus, the filing date of the instant claims 12, 66, 82, 83, 85, 88 and 89 are deemed to be the filing date of the instant application, 14 Nov 2006. The filing date of instant

claims 1-11, 56-65, 84, 86 and 87 are deemed to be the filing date of provisional application 60/541,247, filed 04 Feb 2004. If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Election/Restrictions

Applicant's election with traverse of the invention of Group I, claims 1-12, 56-66, and 82-98, in the reply filed on 04 Jan 2008 is acknowledged. The traversal is on the ground(s) that the amorphous nature of the complex is part of the special technical feature of the cladribine-cyclodextrin complex in a solid oral dosage form. This is not found persuasive because Schultz et al. (US Patent 6,194,395, of record) explicitly discloses a cladribine-cyclodextrin complex in a solid oral dosage form (column 5, lines 50-52). Further, Schultz et al. references the method of making said solid oral dosage form disclosed in WIPO Publication WO97/18839 (cited in PTO-892), which is drawn to the embodiment wherein the melt-extruded forms consist essentially of amorphous material (page 8, lines 14-15). Therefore WIPO Publication WO97/18839 provides evidence that it was recognized in the prior art that the product disclosed by Schultz et al. inherently includes amorphous cladribine-cyclodextrin complex in a solid oral dosage form. While the International Search Report is factually correct in stating that Schultz et al. is silent about specific ratios of cladribine to cyclodextrin and amorphous forms, a

patent need not teach, and preferably omits, what is well known in the art. By referencing WIPO Publication WO97/18839 Schultz et al. demonstrates that the amorphous cladribine-cyclodextrin complex produced by the melt-extrusion method is well known in the prior art. Finally, to address the scientific issue regarding the equilibrium presence of both the inclusion and non-inclusion complex, while the mathematical equation for the equilibrium of the cladribine-cyclodextrin inclusion complex and the cladribine-cyclodextrin non-inclusion complex would be different for cladribine and cyclodextrin in a solvent versus cladribine and cyclodextrin in a molten state, ie. a liquid mixture absent solvent, the equilibrium and thus equilibrium products would still be present.

The requirement is still deemed proper and is therefore made FINAL.

Claims 13-35 and 67-81 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on 04 Jan 2008.

Specification

The disclosure is objected to because of the following informalities:

a) The blanks identifying the provisional patent application numbers on page 23, lines 25 and 27 must be replaced with the application numbers.

b) The minor typographical error "comples" on page 22, line 12.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 11 and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "saturated" in claims 2, 11 and 57 is a relative term which renders the claim indefinite. The term "saturated" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The following definition for "saturated" is provided in the specification, page 10 lines 1-13:

> The term "saturated" when used in conjunction with a complex of cladribine in amorphous cyclodextrin means that the complex is saturated with cladribine, that is, the complex contains the maximum amount of cladribine which can be complexed (by means of both inclusion and non-inclusion complexes) with a given amount of cyclodextrin under the conditions of complexation used. A phase solubility study can be used to provide this information, as described in more detail hereinafter. (Conditions for the complexation are also described in more detail below.) Alternatively, a saturated complex may be arrived at empirically by simply adding cladribine to an aqueous solution of the selected cyclodextrin until no more cladribine goes into solution; ultimately, excess cladribine, if any, is removed (by filtration or centrifugation) and the solution lyophilized to provide the dry saturated complex.

The saturated complex is defined in relation to a maximum amount of cladribine which can be complexed under the conditions of complexation used. However, this amount is defined only empirically. A saturated aqueous solution is invoked with regard to this empirically defined maximum amount of cladribine which can be complexed, but the

claims are drawn to a saturated complex in a solid oral dosage form, not a saturated solution. Therefore one of ordinary skill in the art would not be reasonably apprised of the scope of the invention because the maximum amount would have to be determined empirically for each composition. For the purpose of furthering prosecution, Examiner has interpreted the "maximum amount of cladribine which can be complexed" to be the weight ratio of 1:10 for the cladribine:cyclodextrin complex, based on guidance given on page 31, lines 18-20.

Claim 2 recites the limitation "the complex" in line 2. There is insufficient antecedent basis for this limitation in the claim. It is unclear which complex is referred to by the term "the complex," the inclusion complex (a), the non-inclusion complex (b), both complexes or the complex cladribin-cyclodextrin complex.

Similarly, claim 11 recites the limitation "saturated complexes" in line 3. There is insufficient antecedent basis for this limitation in the claim. It is unclear which complex is referred to by the term "complexes," the inclusion complex (a), the non-inclusion complex (b), both complexes or the complex cladribin-cyclodextrin complex.

The term "a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin" in claim 11 is a relative term which renders the claim indefinite. The term "a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The broadness of the term "a point

located on a phase solubility diagram" does not necessarily render the term indefinite. However, no standard is given for what "phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin" is referred to in the claim, such as what temperature, pressure, or solvent this phase solubility diagram describes. Therefore one of ordinary skill in the art would not be reasonably apprised of the scope of the invention from the term "a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 11, 56-60, 82-90 and 94-98 are rejected under 35 U.S.C. 102(b) as being anticipated by Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) as evidenced by Baert et al. (WIPO Publication WO97/18839, published 29 May 1997, cited in PTO-892).

Schultz et al. discloses a solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin (column 2, lines 31-39), meeting the limitations of instant claims 1 and 56. The disclosed product is substantially identical to a product-by-process meeting the limitations of instant claims 82-90 and 94-96. Schultz et al. discloses the use of β- and γ-cyclodextrins (column 2, lines 56-58) and derivatives

wherein one or more cyclodextrin hydroxy groups are replaced with groups such as methyl, hydroxypropyl, carboxymethyl (column 3, lines 26-27) or sulfobutylcyclodextrins (column 4, lines 22-24), meeting the limitations of instant claims 3-5 and 58-60. The phrase "one or more cyclodextrin hydroxy groups" combined with the absence of specific structural details of which hydroxyl group is substituted with a methyl group meets the limitation of "randomly methylated β-cyclodextrins" of instant claims 3 and 58. Schultz et al. discloses the solid oral dosage form in the form of a tablet (column 5, lines 37-38) including the excipients sorbitol and magnesium stearate (column 6, lines 2-7), disclosing a product that is substantially identical to a product-by-process meeting the limitations of instant claims 97 and 98. Schultz et al. discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, which would lead one of skill in the art to instantly envision a cladribine to cyclodextrin ratio ranging from 15 mg:100 mg to 15mg:500 mg, or 1:6.67 to 1:33.3 by weight (column 6, lines 23-31). These values molar ratios that correspond to "a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin," meeting the limitations of instant claim 11. The language of instant claim 11 as disclosed requires only that the point be located on a phase solubility diagram for said complexes, not that the point be located on the curve defining a saturated complex such as the curve disclosed in the Figure, meaning that any composition according to claim 1 necessarily meets the limitations of instant claim 11 as disclosed. The instant specification suggests that maximum amount of cladribine which can be complexed gives a weight ratio of 1:10 for the cladribine:cyclodextrin complex. Therefore a

composition comprising the cladribine:cyclodextrin complex that contains a cladribine to cyclodextrin ratio of 1:6.67 describes a composition that comprises a "saturated" complex and meets the limitations of instant claims 2 and 57. The open language of "comprising" allows for the presence of uncomplexed cladribine in the composition.

Schultz et al. incorporates-by-reference the method of making said solid oral dosage form (Schultz et al.column 5, lines 50-52) disclosed in WIPO Publication WO97/18839, Baert et al., which provides evidence in the embodiment wherein the melt-extruded forms consist essentially of amorphous material (Baert et al. page 8, lines 14-15). Therefore Baert et al. provides evidence that it was recognized in the prior art that the product disclosed by Schultz et al. inherently includes amorphous cladribine-cyclodextrin complex in a solid oral dosage form.

To address the scientific issue regarding the equilibrium presence of both the inclusion and non-inclusion complex, while the equation for the equilibrium of the cladribine-cyclodextrin inclusion complex and the cladribine-cyclodextrin non-inclusion complex would be different for cladribine and cyclodextrin in a solvent versus cladribine and cyclodextrin in a molten state due to the lack of a solvent, the equilibrium and thus equilibrium products, the cladribine-cyclodextrin inclusion complex and the cladribine-cyclodextrin non-inclusion complex, would still be inherent in the product disclosed by Schultz et al.

Claims 82-90 and 94-98 are drawn to a product-by-process. The disclosed product is substantially identical to the instantly claimed product-by-process, an amorphous solid pharmaceutical oral dosage form comprising cladribine and

cyclodextrin. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-10, 12, 56, 61-66, 82 and 91-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) in view of Baert et al. (WIPO Publication WO97/18839, published 29 May 1997, cited in PTO-892).

Schultz et al. as evidenced by Baert et al. discloses as above. Schultz et al. implicitly discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, or a cladribine to cyclodextrin ratio ranging from 1:6.67 to 1:33.3 by weight (column 6, lines 23-31).

Schultz et al. does not specifically disclose the composition comprising a cladribine to cyclodextrin ratio from about 1:10 to about 1:16 (instant claims 6, 7, 10, 61, 62 and 65), or a ratio of about 1:14 (instant claims 8 and 63) or about 1:11 (instant claims 9 and 64). Schultz et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b) (instant claims 12 and 66). Schultz et al. does not specifically disclose the product-by-process wherein 12.00 parts by weight of cladribine and 172.50 parts by

weight of hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 91 and 93), to give a cladribine to cyclodextrin ratio of 1:14.38.

Schultz et al. does not specifically disclose the product-by-process wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 92), to give a cladribine to cyclodextrin ratio of 1:10.55.

Baert et al. discloses a solid mixture comprising one or more cyclodextrins and an insoluble active ingredient embedded into the cyclodextrin carrier (abstract), and teaches ratios of active ingredient to cyclodextrin of from about 1:100 to 100:1, from about 1:5 and 5:1 and from about 1:3 to 3:1 (page 11, lines 1-5). These ratios are interpreted as mole ratios because Baert et al. teaches the use of different active ingredients with different molecular weights. A mole ratio of active ingredient to cyclodextrin of about 1:3 for cladribine (MW 285.7 g/mol) and β-cyclodextrin (MW 1135 g/mol) gives a ratio by weight of approximately 1:11.9. The ratio of 1:11.9 meets the limitation of both a ratio of about 1:11 and a ratio of about 1:14 according to the non-limiting definition of "about" as a variance of 20% provided in the instant specification page 9, lines 6-11.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin disclosed by Schultz et al. in the ratios of cladribine and cyclodextrin taught by Baert et al. One of ordinary skill in the art would be motivated to combine the Schultz et al. and Baert et al. because Schultz et al. incorporates-by-

reference Baert et al. and because Baert et al. suggests that improving a similar product according to the teachings of Baert et al. has beneficial properties such as high bioavailability and dissolution rate (Baert et al. page 7, lines 25-27). One of ordinary skill in the art would have an expectation of success because the ratios taught by Baert et al. fall within the range of ratios that is implicitly disclosed by Schultz et al. Schultz et al. in view of Baert et al. does not teach the specific cladribine to cyclodextrin ratios of 1:14.38 or 1:10.55, however these ratios are encompassed by the prior art and Baert et al. suggests optimization of the ratio (Baert et al. page 11, lines 1-5). See also MPEP 2144.05 II.A, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." Schultz et al. in view of Baert et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b). However, it is well known in the art that the formation of an inclusion complex from a non-inclusion complex is an equilibrium process, and the position of this equilibrium is dependent on the concentrations of the cladribine and cyclodextrin. This molecular inclusion equilibrium is a process inherent in the formation of the inclusion complex in both aqueous solutions and hot melt liquid mixtures, and Baert et al. teaches variation of the ratio of cladribine to cyclodextrin and hence their relative concentration.

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which

there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed, namely the position of the equilibrium process governing formation of an inclusion complex and a non-inclusion complex. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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